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## (54) SUBSTITUTED p-MENTHANECARBOXAMIDES AND COMPOSITIONS CONTAINING THEM


(71) We, WILKINSON SWORD LIMITED, a British Company, of Sword Works, Southfield Road, London, W.4, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

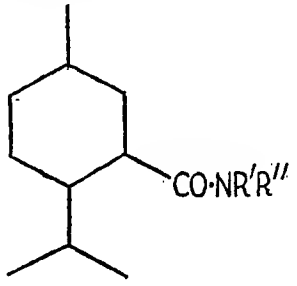

This invention relates to a novel group of compounds having a physiological cooling effect on the skin and on the mucous membranes of the body, particularly, the nose, mouth, throat and gastrointestinal tract and to ingestible, topical and other compositions containing them.

Menthol is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (menthol being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices and mouthwashes, and as a component in a wide range of toiletries, liniments and lotions for topical application.

It is well established that the "cooling" effect of menthol is a physiological effect due to the direct action of menthol on the nerve endings of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Although menthol is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and its relative volatility.

In accordance with the present invention, we have discovered a novel group of compounds having a pronounced physiological cooling effect, which have little or no odour, and which are of relatively low volatility and substantially non-toxic. The compounds of this invention are N-substituted *p*-menthane-3-carboxamides of the formula (I):




where

R¹, when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms;

R″, when taken separately is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when R′ is hydrogen R″ may also be an aryl radical of up to 10 carbon atoms and selected from substituted phenyl, phenalkyl, naphthyl and substituted naphthyl, and pyridyl; and

R′ and R″ when taken together, represent a cyclic or heterocyclic group of up to 25 carbon atoms.

In the above definitions " aliphatic " is intended to include any straight-chained, branched-chained or cyclic radical free of aromatic unsaturation, and thus embraces alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, hydroxyalkyl, acyloxyalkyl, alkoxy, alkoxyalkyl, aminoalkyl, acylaminoalkyl, carboxyalkyl and similar combinations. " Aryl " is intended to include any radical containing aromatic unsaturation and includes alkaryl, aralkyl and like combinations.

The invention also provides compositions, in particular ingestible compositions and compositions for topical application, capable of stimulating the cold receptors of the nervous system of the human body comprising an effective amount of a cold receptor stimulant and a carrier therefor, the stimulant comprising one or more of the above defined N-substituted - *p* - menthane - 3 - carboxamides.

Particular compositions provided within the scope of this invention are:

1) Comestible compositions comprising an edible base, a flavourant or colourant, and a cold receptor stimulant as defined above.
2) Beverages comprising a potable base, a flavourant or colourant, and a cold receptor stimulant as defined above.
3) Lotions comprising an aqueous alcoholic or aqueous-alcoholic carrier, an adjuvant selected from the following: a colourant, an antiseptic or an odourant, and a cold receptor stimulant as defined above.
4) Dentifrices comprising an abrasive, a detergent or foaming agent and a cold receptor stimulant.
5) Toilet preparations, e.g. soaps and creams, comprising an oleaginous or surfactant base and a cold receptor stimulant as above defined.
6) Pharmaceutical preparations comprising an antacid and a cold receptor stimulant as above defined.
7) Toilet articles, e.g. cleansing tissues and toothpicks, comprising a carrier impregnated or coated with a cold receptor stimulant as defined.

The N - substituted - *p* - menthane - 3-carboxamides of the invention may be readily prepared by conventional methods, such as by the reaction of the corresponding acid chloride (obtained by reacting *p* - menthane-3 - carboxylic acid with thionyl chloride) with the appropriate mono- or di-substituted amine. The reaction will usually be carried out in solution in the presence of a hydrogen chloride receptor e.g. sodium hydroxide. The reaction proceeds smoothly at room temperature.

The compounds of this invention exhibit both geometric and optical isomerisation and, depending on the starting materials and the methods used, the compounds of this invention may be isomerically pure, i.e. consisting of one geometric or optical isomer, or they may be isomeric mixtures, both in the geometric and optical sense.

As is well known, the basic *p*-menthane structure is a chair-shaped molecule which can exist in *cis* or *trans* forms. Substitution of the carboxamide group into the 3-position gives rise to four configurational or geometric isomers depending upon whether the substitution is axially or equatorially into the *cis* or *trans* isomer, the four isomers being related as menthol is to neomenthol, isomenthol and neoisomenthol. In general it is found that in the compounds of this invention the equatorially substituted carboxamides have the greater cooling effect than the axial compounds and are to be preferred.

Substitution of the carboxamide group in the 3-position of the *p*-menthane structure also gives rise to optical isomerism, each of the above-mentioned four geometric isomers existing in *d*, *l* and *dl* forms. The physiological cooling effect is found, in most cases, to be greater in the *l*-form than in *d*-form, and in some cases substantially greater. The compounds derived from the *l* form of *p*-menthane - 3 - carboxylic acid are therefore preferred.

The cooling sensation created by the compounds of the invention on the skin and mucous membranes, for example, in the mouth, varies both in intensity and longevity from compound to compound.

When either R′ and R″ is aliphatic the preferred values are $C_1$—$C_9$ straight or branched chain hydroxyalkyl or aminoalkyl and $C_1$—$C_4$ acylated derivatives thereof, and —$C_nH_{2n}COR'''$ or —$C_nH_{2n}COOR'''$, where —$C_nH_{2n}$ is a straight or branched chain alkylene radical in which n is an integer of from 1—6 and R‴ is hydrogen or a $C_1$—$C_8$ alkyl or hydroxyalkyl group, preferably a $C_1$—$C_4$ straight chain alkyl group.

In general the monosubstituted compounds, i.e. where R′ is H, are preferred although disubstituted compounds where R′ and R″ are both $C_1$—$C_3$ alkyl also show a very pronounced cooling effect. Most preferred of all are compounds where R′ is H and R″ is $C_1$—$C_3$ alkyl, $C_1$—$C_4$ hydroxyalkyl, or

—$CH_2COOR'''$, where R''' is $C_1$—$C_4$ alkyl.

Also included within the scope of this invention are compounds where R' is H and R'' is hydroxy or substituted phenyl, e.g. alkylphenyl, hydroxyphenyl, alkoxyphenyl, halophenyl, of up to 10 carbon atoms, phenalkyl or substituted phenalkyl e.g. benzyl, naphthyl or substituted naphthyl, and compounds where R' and R'' are joined to form a cyclic group. When so joined R' and R'' preferably represent an alkylene chain, optionally interrupted by oxygen, which together with the nitrogen atom to which R' and R'' are attached forms a 5- or 6-membered heterocyclic ring.

Compounds falling within the scope of formula I and of particular note are given in Table I.

TABLE I

| R' | R'' | m.p. °C. | b.p. °C. |
|---|---|---|---|
| H | —$CH_3$ | 95—7° | |
| " | —$C_2H_5$ | 82.5—84.5° | |
| " | —$C_3H_7$(n) | 65—7° | |
| " | —$C_5H_7$(iso) | 94—6° | |
| " | —$CH_2CH_2OH$ | | 160°/.1 mm. |
| " | —$(CH_2)_3OH$ | | 170°/.1 mm. |
| " | —$CH_2CH(OH)CH_3$ | | 184°/.1 mm. |
| " | —$C(CH_3)_2CH_2OH$ | 123° | |
| " | —$CH_2COOC_3H_7$(n) | | 170°/.1 mm. |
| " | —$CH_2COOC_2H_5$ | | 150°/.1 mm. |
| —$CH_3$ | —$CH_3$ | | 56—57°/0.01 mm. |
| —$C_2H_5$ | —$C_2H_5$ | | 78—80°/0.05 mm. |

Alternative compounds of formula I and shown to have a cooling effect in accordance with this invention are given in Table II.

TABLE II

| R′ | R″ | m.p. °C. | b.p. °C. |
|---|---|---|---|
| H | —$C_4H_9$(n) | 88—9° | |
| ,, | —$C_4H_9$(iso) | 111—112° | |
| ,, | —$C_4H_9$ (sec) | 116—119° | |
| ,, | —$C_4H_9$(tert) | 145—146° | |
| ,, | —$CH_2COOH$ | | |
| —$CH_2CH_2OH$ | —$CH_2CH_2OH$ | | |
| H | —OH | 124—125° | |
| —$(CH_2)_4$— | | 54—56° | |
| —$(CH_2)_5$— | | | 102—104°/.05 mm. |
| | —$CH_2CH_2OCH_2CH_2$— | | 101—103°/.05 mm. |
| | —$CH_2CH_2NHCH_2CH_2$— | | |
| —H | $CH_2PH$ | 106—107° | |
| —H | —$CH_2C{\equiv}CCH_2OH$ | | 180°/.1 mm. |
| ,, | —$CH_2CH_2NH_2$ | | |
| ,, | —$CH(CH_3)COOC_2H_5$ | | 160°/.1 mm. |
| ,, | —$(CH_2)_6OH$ | | 220°/.1 mm. |
| ,, | —$CH(C_2H_5)CH_2OH$ | | 190°/.1 mm. |
| ,, | —$CH_2CH_2COOC_2H_5$ | | 152°/.1 mm. |
| ,, | —$CH_2COOCH_3$ | | 130—140°/.1 mm. |
| ,, | —$CH(CH_3)CH_2COOC_2H_5$ | | 164°/.1 mm. |
| ,, | —$CH_2OH$ | 141—2° | |
| ,, | —$CH_2CH_2OCOCH_3$ | | 159—162°/.1 mm. |
| ,, | —$C_5H_{11}$(n) | 80—82° | |
| ,, | —$C_6H_4OMe$(p) | 177°C. | |
| ,, | —$C_6H_4OH$(p) | | 230°/.1 mm. |

The compounds of this invention find utility in a wide variety of compositions for consumption by or application to the human body. Broadly speaking, these compositions can be divided into comestible and topical compositions, both terms being taken in their broadest possible sense. Thus comestible is to be taken as including not only foodstuffs and beverages taken into the mouth and swallowed, but also other orally ingested compositions taken for reasons other than their nutritional value, e.g. indigestion tablets, antacid preparations and laxatives. Comestible compositions are also to be taken to include edible compositions taken by mouth, but not necessarily swallowed, e.g. chewing gum. Topical compositions are to be taken as including not only compositions such as perfumes, powders and other toileteries, lotions, liniments, oils and ointments applied to the external surfaces of the human body, whether for medical or other reasons, but also compositions applied to, or which, in normal usage, come in contact with, internal mucous membranes of the body, such as those of the nose, mouth, or throat, whether by direct or indirect application or inhalation, and thus include nasal and throat sprays, dentifrice, mouthwash and gargle compositions. Topical compositions is also to be taken to include toilet articles such as cleansing tissues and toothpicks.

The compositions of this invention will contain an amount of the N - substituted - *p*-menthane - 3 - carboxamide sufficient to stimulate the cold receptors in the areas of the skin or mucous membrane with which the compositions come into contact and thereby promote the desired cold sensation. As indicated, the degree and longevity of cooling sensation varies from compound to compound and therefore the quantity of stimulant used in each composition will vary widely. As a guide, it may be said that, with the more active compounds of the invention, a significant cooling sensation, which, in some cases, may persist for several hours, is achieved upon application to the skin of as little as 0.05 ml of a 0.2 weight percent solution of the active ingredient in ethanol. For the less active compounds a significant cooling effect is achieved only with more concentrated solutions, e.g. 5.0% by weight or more of the active ingredient. It must also be admitted that such skin tests are somewhat subjective, some individuals experiencing a greater or lesser cooling sensation than others when subjected to the same test.

In formulating the compositions of this invention the N - substituted - *p* - menthane-3 - carboxamide will usually be incorporated into a carrier which may be completely inert or which may be or contain other active ingredients. A wide variety of carriers will be suitable, depending upon the end use of the composition, such carriers including solids, liquids, emulsions, foams and gels. Typical carriers for the N - substituted - *p* - menthane-3 - carboxamides include aqueous or alcoholic solutions; oils and fats such as hydrocarbon oils, fatty acid esters, long chain alcohols and silicone oils; finely divided solids such as starch or talc; cellulosic materials such as paper tissue; low-boiling hydrocarbons and halohydrocarbons used as aerosol propellants; gums and natural or synthetic resins.

In most compositions according to the invention the carrier will be or contain as an adjuvant one or more of the following: an antacid, antiseptic or analgesic, a flavourant, colourant, or odourant, or a surfactant.

The following illustrate the range of compositions into which the compounds of this invention can be incorporated:

1. Edible or potable compositions including alcoholic and non-alcoholic beverages, confectionery, chewing gum; cachous; ice cream; jellies.
2. Toiletries including after shave lotions, shaving soaps, creams and foams, toilet water, deodorants and antiperspirants, " solid colognes ", toilet soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouthwashes, hair tonics, eyedrops.
3. Medicaments including antiseptic ointments, pile ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, oral analgesics.
4. Miscellaneous compositions such as water soluble adhesive compositions for envelopes, postage stamps and adhesive labels.

In addition to the above, the compounds of this invention are also useful when included in the composition of tobacco preparations and tobacco filters, as disclosed in our Divisional Application No. 40395/73 (Serial No. 1,351,762).

Particular preparations according to the invention are discussed in more detail below.

*Edible and Potable Compositions.*

The edible and potable compositions of this invention will contain the N - substituted - *p*-menthane - 3 - carboxamide in combination with an edible carrier and usually a flavouring or colouring agent. The particular effect of the amides of the invention is to create a cool or fresh sensation in the mouth, and in some cases, even in the stomach, and therefore the amides find particular utility in sugar-based confectionery such as chocolate, boiled sweets, mints and candy, in ice cream and jellies and in chewing gum. The formulation of such confections will be by ordinary techniques and according to conventional

recipes and as such forms no part of this invention. The amide will be added to the recipe at a convenient point and in amount sufficient to produce the desired cooling effect in the final product. As already indicated, the amount will vary depending upon the particular amide, the degree of cooling effect desired and the strength of other flavourants in the recipe. For general guidance, however, amounts in the range .01 to 5% by weight based on the total composition will be found suitable.

Similar considerations apply to the formulation of beverages. Generally speaking the amides will find most utility in soft drinks, e.g. fruit squashes, lemonade and cola, but may also be used in alcoholic beverages. The amount of amide used will generally be in the range .005 to 2.5% by weight based on the total composition.

*Toiletries*

Because of the cooling sensation imparted to the skin, a major utility of the amides of this invention will be in a wide range of toilet preparations and toilet articles. The particular preparations discussed below are to be taken as exemplary.

A major utility will be in after shave lotions and toilet water where the amide will be used in alcoholic or aqueous alcoholic solution, such solutions usually also contain a perfume or mild antiseptic or both. The amount of amide added to the formulation will usually be in the range 0.1 to 3.0% by weight based on the total composition.

Another field of utility will be in soaps, shampoos and bath oils where the amides will be used in combination with an oil or fat or a natural or synthetic surfactant, e.g. a fatty acid salt or a lauroylsulphate salt, the composition usually also containing an essential oil or perfume. The range of soap compositions will include soaps of all kinds, e.g. toilet soaps, shaving soaps and shaving foams. Usually the amide will be added to the formulation in amount of from 0.5 to 4.0% by weight.

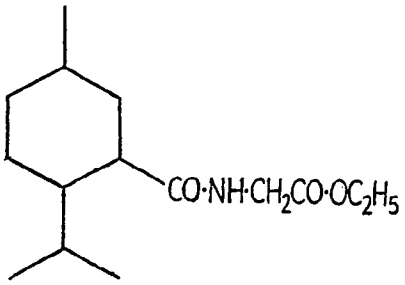
A further class of toilet compositions into which the compounds of this invention may be incorporated includes cosmetic creams and emollients, such creams and emollients usually comprising a base emulsion and optionally a range of ingredients such as wax, preservative, perfume, antiseptics, astringents and pigments. Also included within this class are lipstick compositions such compositions usually comprising an oil and wax base into which the amide can be incorporated along with the conventional ingredients, i.e. pigments and perfumes. Once again the formulation of such compositions, apart from the incorporation of the amide, usually in an amount of from 0.01 to 5.0% by weight, is conventional.

Compositions for oral hygiene containing the cold receptor stimulants of this invention include mouthwash, gargle and dentifrice compositions. The first two may be considered together and will usually comprise an aqueous, alcoholic or aqueous-alcoholic solution of an antiseptic often coloured or flavoured for palatability, to which the amide is added in an amount of from 0.01 to 0.50% by weight.

Dentifrice compositions may be of the solid block, powder paste or liquid type and will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate, aluminium hydroxide or other similar materials well known in the art, and a detergent or foaming agent. Optional ingredients which may also be included are flavouring agents and colourants, antiseptics, lubricants, thickeners, emulsifiers or plasticizers. A typical toothpaste formulation to which the amides of the present invention may be added to give a fresh, cool sensation in the mouth, consists of:,

EXAMPLE II.

Preparation of N - *p* - Menth - 3 - Oylglycine Ethyl Ester




Sodium bicarbonate (8.4 g., 0.1 mole) and glycine ethyl ester hydrochloride (7 g. 0.05 mole) were dissolved in water (100 ml.), and a solution of *p* - menth - 3 - oyl chloride (10 g., 0.05 mole) in ether (50 ml.) was added and the mixture stirred vigorously at room temperature for 2 hours. At the end of this time the ether layer was separated and dried ($MgSO_4$). Removal of the solvent left an oily solid (12.3 g.). This was distilled under reduced pressure to yield *N - p - menth - 3 - oylglycine ethyl ester,* bp. 150—2°/0.1 mm. as a colourless liquid which rapidly solidified.

EXAMPLE III.

Preparation of N - (2 - Hydroxyethyl) - *p*-Menthane - 3 - Carboxamide

A solution of *p* - menth - 3 - oyl chloride prepared as in Example I (4.0 g., 0.020 moles) in chloroform (30 ml.) was added dropwise to a stirred solution of ethanolamine (3 g., 0.043 moles) in chloroform (50 ml.). The reaction mixtures becomes warm, goes cloudy and finally a yellow oil starts to separate out. After stirring for 2 hours at room temperature the mixture was poured into water. The organic layer was separated, washed with dilute $H_2SO_4$, and dried ($MgSO_4$). Removal of the solvent left a viscous oil (3.8 g.). This was distilled under vacuum to yield *N - (21 hydroxyethyl) - p - menthane - 3 - carboxamide* as a colourless very viscous oil, b.p. 160°/0.1 mm.

EXAMPLE IV.

Preparation of N - (3 - Hydroxypropyl) - *p*-Menthane - 3 - Carboxamide

The procedure of Example III was repeated using propanolamine in place of the ethanolamine. *N - (3 - hydroxpropyl) - p - menthane-3 - carboxamide* was obtained as a very viscous oil, b.p. 170°/0.1 mm.

EXAMPLE V.

Preparation of N,N - Dimethyl - *p*-Menthane - 3 - Carboxamide

A mixture of *p* - menthane - 3 - carboxylic acid (1.84 g.) and thionyl chloride (5 ml.) was heated under reflux for 2 hours. The excess of thionyl chloride was then removed *in vacuo.* The residue was dissolved in dry diethyl ether (25 ml.) and this solution was added slowly with stirring and cooling to a solution of dimethylamine (0.46 g.) and sodium hydroxide (0.4 g.) in water (25 ml.). After stirring at room temperature for 1 hour, the ether layer was separated and the aqueous layer was extracted with a further quantity (25 ml.) of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to leave an oil. This oil was distilled to give *N,N - dimethyl - p-menthane - 3 - carboxamide* as a colourless oil, b.p. 56—7°/0.01 mm.

EXAMPLE VI.

Preparation of N,N - Bis(2 - Hydroxyethyl)-*p* - Menthane - 3 - Carboxamide

A solution of *p* - menth - 3 - oyl chloride (4.0 g., 0.020 moles) in chloroform (30 ml.) was added dropwise to a stirred solution of diethanolamine (4.2 g., 0.044 moles) in chloroform (50 ml.). The reaction mixture goes cloudy and a yellow oil separates out. After 2 hours at room temperature, the yellow oil (upper layer) was separated. Infra red spectographic analysis indicated this to be

$$(HOCH_2CH_2)_2\ NH_2^+Cl^-.$$

Removal of the chloroform left a viscous oil (6 g.). Thin layer chromatography ($CHCl_3$ and $CHCl_2$ + 10% $CH_3OH$) indicated it to consist of one major component and a minor component of larger $R_f$ value. This was separated by column chromatography on neutral alumina (activity 1). Eluting with chloroform (200 ml.) removed the minor component and the major product was eluted from the column with chloroform + 5% methanol. The major component was shown to be N,N-bis (2-hydroxyethyl) - *p* - menthane - 3 - carboxamide.

Analysis:

Found C: 65.8; H: 10.6; N: 5.2.
Calculated C: 66.4; H: 10.7; N: 5.2.

EXAMPLE VII.

Preparation of N - *p* - Menth - 3 - Oylglycine *n*-Propyl Ester

Following the procedure of Example II *p*-menth - 3 - oyl chloride (2.0 g., 0.01 moles), was reacted with glycine propyl ester hydrochloride (1.5 g., 0.01 moles) and sodium bicarbonate (1.6 g., 0.02 moles). The crude product was distilled b.p. 170°/0.1 mm. (After distillation the product rapidly solidifies). (Found: C: 68.2; H: 10.6; N: 5.0. $C_{16}H_{29}NO_3$ requires, C: 67.8; H: 10.6; N: 4.9).

| Ingredient | % by weight |
|---|---|
| Precipitated chalk | 20 |
| Fine Silica | 15 |
| Magnesium Carbonate | 4 |
| Dicalcium Phosphate | 6 |
| Surfactant e.g. alkylated aryl sulfonate | 8 |
| Starch glycerite | 18 |
| Mineral Oil | 1 |
| Mucilage | 4 |
| Syrup | 12 |
| Glycerin | 12 |

The amount of amide added in such compositions will generally be from 0.1 to 1.0% by weight based on the total composition.

Also of interest are cleansing tissues comprising a fibrous carrier impregnated with an alcoholic solution of an N-substituted-*p*-menthane carboxamide.

*Medicaments*

Because of their cooling effect on the skin and on the mucous membranes of the mouth, throat and nose and of the gastrointestinal tract the amides of this invention may be used in a variety of oral medicines, nasal and throat sprays, and topical compositions, particularly where a counter-irritant is required. In particular the amides may be formulated into antacid and indgestion remedies, in particular those based on sodium bicarbonate, magnesium oxide, calcium or magnesium carbonate, aluminium or magnesium hydroxide or magnesium trisilicate. In such compositions the amide will usually be added in an amount of from 0.01 to 0.5% by weight.

The amides may also be included in oral analgesic compositions e.g. with acetylsalicyclic acid or its salts, and in nasal decongestants e.g. those containing ephedrine.

Compounds and compositions of this invention are illustrated by the following Examples. All temperatures are given in degrees Centigrade. The *p* - menthane - 3 - carboxylic acid used as starting material in all the Examples was itself prepared by the carbonation of the Grignard reagent derived from l-menthol according to known techniques.

EXAMPLE I.

Preparation of N-Ethyl *p*-Menthane-3-Carboxamide

*p* - Menthane - 3 - carboxylic acid (1.84 g.), was heated under reflux with thionyl chloride (4 ml.) for 3 hours. The excess of thionyl chloride was then distilled off *in vacuo*. The crude product *p* - menth - 3 - oyl chloride was dissolved in diethyl ether (25 ml.) and the thereal solution was added with stirring and cooling to a solution of ethylamine (1.0 ml of 70% w/s solution in water) and sodium hydroxide (0.4 g.) in water (25 ml.). The mixture was stirred for one hour and the ethereal layer was then separated. The aqueous layer was washed with ether (25 ml.) and the combined ethereal solution was washed with dilute hydrochloric acid and then water. The ether solution was dried ($MgSO_4$) and evaporated to give a white crystalline solid. This solid was recrystallised from acetone: water (9 : 1) by dissolving the crystals at room temperature and then cooling to produce *N-ethyl - p - menthane - 3 - carboxamide* as a white crystalline solid, fp. 82.5°—84.5°. $[\alpha]_D^{25} = -46.7°$ (concentration—2.14 gms. per 100 ml. in ethanol).

EXAMPLE VIII.

Preparation of N - (2 - hydroxy - *n* - Propyl)-*p* - Menthane - 3 - Carboxamide

*p*-Menth-3-oyl chloride (3.0 g.) was reacted with isopropanolamine (3.0 g.) according to the procedure of Example III. The product, N - (2 - hydroxy - *n* - propyl) - *p*-menthane - 3 - carboxamide, was obtained as a viscous oil, boiling point: 184°/0.1 mm.

EXAMPLE IX.

Preparation of N - (1,1 - Dimethyl - 2-Hydroxyethyl) - p - Menthane - 3 - Carboxamide

*p*-Menth-3-oyl chloride (3.0 g.) was reacted with 2 - amino - 2 - methyl - propan-1 - ol (3.0 g.) according to the procedure of Example III. Product N - (1,1 - dimethyl - 2-hydroxyethyl) - *p* - menthane - 3 - carboxamide was obtained as a crystalline solid which was recrystallised from aqueous methanol. M.p. 123°.

EXAMPLE X.

Preparation of N,N - Diethyl - *p* - Menthane-3 - Carboxamide.

Following the procedure of Example V, *p*-menthane - 3 - carboxylic acid (1.84 g.) was reacted with thionyl chloride and the *p*-menth-3-oyl chloride then reacted with diethylamine (0.74 g.) in the presence of sodium hydroxide (0.4 g.). The product N,N - diethyl - *p*-menthane - 3 - carboxamide was recovered.

EXAMPLE XI.

Preparation of N - Tert - Butyl - *p*-Menthane - 3 - Carboxamide

Following the procedures of Example I, *p*-menthane - 3 - carboxylic acid (1.84 g.) was reacted with thionyl chloride and the crude *p* - menth - 3 - oyl chloride recovered and reacted with tert butylamine (0.74 g.) in the presence of sodium hydroxide (0.4 g.). The crystalline product, N - tert. - butyl - *p*-menthane - 3 - carboxamide, was recovered and recrystallised from aqueous ethanol. M.p. 145—146°.

EXAMPLE XII.

Preparation of N - Methyl - *p* - Menthane - 3-Carboxamide.

The procedures of Example I were repeated using methylamine (0.32 g.) in place of the ethylamine. Crystalline product N - methyl-*p* - menthane - 3 - carboxamide was recovered, m.p. 95—97°.

EXAMPLE XIII.

Preparation of N - (*p* - Menth - 3 - Oyl) Morpholine

The procedure of Example V was repeated using morpholine (0.88 g.) in place of the dimethylamine. The product N - (*p* - menth-3 - oyl) morpholine was recovered.

EXAMPLE XIV.

Preparation of *p*-Menthane Hydroxamic Acid

Hydroxylamine hydrochloride 1.0 g., (0.014 mole) and sodium bicarbonate 3.4 g. (0.04 mole) were dissovled in 30 ml. water in a flask filled with reflux condenser and magnetic stirrer. When evolution of $CO_2$ had ceased 20 ml. of ether was added and the solution stirred vigorously. *p* - Menth - 3 - oyl chloride 2 g. (0.001 mole) in 15 ml. of ether, was added dropwise down the condenser.

After all of the acid chloride had been added, spectra were taken of samples of the ether layer, at 15 minute intervals. When the characteristic acid chloride absorption at 1800 $cm^{-1}$ was no longer present in the spectra the reaction was complete. The ether layer was carefully separated from the aqueous layer, and evaporated to dryness, yielding 2 g. of white powder.

The product, *p*-menthane hydroxamide acid, was recrystallised from an ethanol/water mixture.

EXAMPLE XV.

Preparation of N - (4 - Hydroxybut - 2-Ynyl) - *p* - Menthane - 3 - Carboxamide

Sodium bicarbonate (2.5 g.) and 4 - amino-but - 2 - yl - 1 - ol hydrochloride (2.5 g.) were dissolved in water (60 ml.) and a solution of *p* - menth - 3 - oyl chloride in ether (100 ml.) added. The mixture was stirred vigorously for two hours and the ether layer separated and dried over $MgSO_4$. Evaporation of the ether gave N - (4 - hydroxybut - 2-ynyl) - *p* - menthane - 3 - carboxamide as a very viscous liquid: b.p. 180°/0.1 mm.

EXAMPLE XVI.

Preparation of N - (*p* - Hydroxyphenyl) - *p*-Menthane - 3 - Carboxamide

*p* - Menth - 3 - oyl chloride (2.0 g.) and p-aminophenol (2.2 g.) were stirred for four hours at room temperature in ether (100 ml.). Product N - (*p* - hydroxyphenyl) - *p* - menthane - 3 - carboxamide was recovered.

In order to determine the physiological cooling effect of the compounds of this invention on the human body, the compounds prepared in Examples I—XVI were formulated as 0.2 wt. per cent solutions in ethanol and 0.05 ml. of each solution rubbed onto the faces of a selected panel of people in the region of the cheek bone. The test subjects were asked to report on cooling effect noticed after a period of two minutes, i.e. after cooling effects attributable to evaporation of the alcoholic carrier had worn off. The results are tabulated below in Table III, the cooling effect being rated on an arbitrary scale of one, two or three stars, representing respectively a weak but noticeable effect, a moderate cooling effect, and a very strong cooling effect.

TABLE III

| Compound Example | Cooling Effect |
|---|---|
| I | *** |
| II | *** |
| III | ** |
| IV | ** |
| V | ** |
| VI | * |
| VII | *** |
| VIII | ** |
| IX | *** |
| X | ** |
| XI | *** |
| XII | *** |
| XIII | * |
| XIV | ** |
| XV | ** |
| XV | ** |

Compositions according to the invention are illustrated by the following Examples, all percentages are by weight.

## EXAMPLE XVII.

*Aerosol Shaving Soap*

An aerosol shaving soap composition was formulated according to the following recipe:

| | |
|---|---|
| Stearic acid | 6.3% |
| Laurice acid | 2.7 |
| Triethanolamine | 4.6 |
| Sodium carboxymethyl cellulose | 0.1 |
| Sorbitol | 5.0 |
| Perfume | 0.4 |
| Water | to 100 |

The composition was prepared by fusing the acids in water, adding the triethanolamine, cooling and adding the other constituents. To the mixture was then added 1.0%, based on the total composition of N,N - dimethyl - *p*-menthane - 3 - carboxamide. The composition was then packaged in an aerosol dispenser under pressure of a butane propellant.

When used in shaving a fresh cool sensation was distinctly noticeable on the face.

## EXAMPLE XVIII.

*After Shave Lotion*

An after shave lotion was prepared according to the following recipe by dissolution of the ingredients in the liquid and cooling and filtering:

| | |
|---|---|
| Denatured Ethanol | 75% |
| Diethyl phthalate | 1.0 |
| Propylene Glycol | 1.0 |
| Lactice Acid | 1.0 |
| Perfume | 3.0 |
| Water | to 100% |

Into two separate samples of the base lotion were added 2.0% by weight based on the total composition of N - ethyl - *p* - menthane-

3 - carboxamide and N,N - dimethyl - *p*-menthane - 3 - carboxamide, each into a different one of the two samples.

When applied to the face a clearly noticeable cooling effect became apparent after a short interval of time.

## EXAMPLE XIX.

*Toilet Water*

A toilet water was prepared according to the following recipe:

| | |
|---|---|
| Denatured ethanol | 75.0% |
| Perfume | 5.0% |
| Water | to 100% |

To the recipe was added 3.0%, based on the total composition, of N - *p* - menth - 3-oylglycine methyl ester.

As with the after shave lotion, a cooling effect was clearly noticeable on the skin well after the termination of any cooling effect attributable to the evaporation of the alcoholic carrier.

## EXAMPLE XX.

*Deodorant composition*

A deodorant composition suitable for formulation and dispensing as an aerosol under pressure of a suitable propellant was formulated according to the following recipe:

| | |
|---|---|
| Denatured ethanol | 96.9% |
| Hexachlorophene | 2.0% |
| Isopropyl myristate | 1.0% |
| Perfume | 0.1% |

To the composition was added 1.3% by weight of N - methyl - *p* - menthane - 3-carboxamide. Application of the final composition gave rise to a definite cooling sensation on the skin.

## EXAMPLE XXI.

*Hair Shampoo*

Sodium lauryl ether sulphate, 10 g., was dispersed in 90 g. water in a high speed mill. To the dispersion was added 3.3% by weight of N - (2 - hydroxy - n - propyl) - *p*-menthane - 3 - carboxamide. When the hair is washed using the shampoo a fresh, cool sensation is noticed in the scalp.

## EXAMPLE XXII.

*Lipstick*

0.06% by weight of N - (*p* - menth - 3 - oyl) glycine was incorporated into a proprietary lipstick by melting the lipstick, adding the compound, and allowing the lipstick to resolidify. When applied to the lips a persistent cooling effect is clearly noticeable.

## EXAMPLE XXIII.

*Solid Cologne*

A solid cologne was formulated according to the following recipe:

| | |
|---|---|
| Denatured ethanol | 74.5% |
| Propylene glycol | 3.0% |
| Sodium stearate | 5.0% |
| Perfume | 5.0% |
| Water | to 100% |

The sodium stearate was dissolved by stirring in a warm mixture of the ethanol propylene glycol and water. To the solution was added the perfume and 3.0% of N - (2 - hydroxy-n - propyl) - *p* - menthane - 3 - carboxamide and the mixture then allowed to solidify into a waxy cake.

When applied to the forehead a very strong and long lasting cooling effect is obtained.

## EXAMPLE XXIV.

*Hair tonic*

A hair tonic was formulated containing:

| | |
|---|---|
| Denatured ethanol | 84.5% |
| Castor oil | 14.0% |
| Resorcinol | 0.5% |
| Perfume | 1.0% |

The castor oil, resorcinol and perfumes were dissolved in the ethanol component and to the solution was added 2.0% of N - (*p* - menth-3 - oyl) glycine methyl ester. When rubbed on the scalp a cooling effect is noticed.

## EXAMPLE XXV.

*Eye-Lotion*

An eye lotion was prepared containing the following ingredients:

| | |
|---|---|
| Witch Hazel | 12.95% |
| Boric Acid | 2.00 |
| Sodium Borate | 0.50 |
| Allantoin | 0.05 |
| Salicyclic Acid | 0.025 |
| Chlorobutanol | 0.02 |
| Zinc Sulphate | 0.004 |
| Water | to 100% |

To the formulation was added 0.003%, based on the total composition, of N - (2 - hydroxyethyl) - *p* - menthane carboxamide. When used to bathe the eyes a cool fresh sensation is apparent on the eyeball and eyelids.

## EXAMPLE XXVI.

*Mouthwash*

A concentrated mouthwash composition was prepared according to the following recipe:

| | |
|---|---|
| Ethanol | 3.0% |
| Borax | 2.0 |
| Sodium bicarbonate | 1.0 |
| Glycerol | 10.0 |
| Flavourant | 0.4 |
| Thymol | 0.03 |
| Water | to 100% |

To the composition was added 0.1% of N - n-propyl - *p* - menthane - 3 - carboxamide.

When diluted with approximately 10 times its own volume of water and used to rinse the mouth a strong and long lasting cooling effect is obtained in the mouth.

## EXAMPLE XXVII.

*Toothpaste*

The following ingredients were mixed in a blender:

| | |
|---|---|
| Dicalcium phosphate | 48.0% |
| Sodium lauryl sulphate | 2.5 |
| Glycerol | 24.8 |
| Sodium carboxymethyl cellulose | 2.0 |
| Citrus flavourant | 1.0 |
| Sodium saccharin | 0.5 |
| Water | to 100% |

Shortly before completion of the blending operation 0.5% by weight of N - (*p* - menth-3 - oyl)morpholine was added to the blender.

When applied as a toothpaste, a strong cooling effect is noticed in the mouth.

This Example illustrates how the physiological cooling effect of the compounds of this invention varies according to the locality of application. When applied to the skin as an alcoholic solution, the cooling effect of N - (*p*-menth - 3 - oyl)morpholine is relatively weak. When applied to the mucous membranes of the mouth the cooling effect is very pronounced.

## EXAMPLE XXVIII.

*Toothpicks*

The tip of a wooden toothpick was impregnated with an alcoholic solution containing N - ethyl - *p* - menthane - 3 - carboxamide in sufficient amount to deposit on the toothpick 0.01 mg. of the carboxamide. The impregnated toothpick was then dried. When placed on the tongue there is no detectable taste, however, a distinct cooling effect is noticeable after a short period of time.

## EXAMPLE XXIX.

*Talcum Powder*

A talcum powder was prepared by grinding together the following:

| | |
|---|---|
| Low micron talc | 90% |
| Zinc stearate | 5% |
| Starch | 5% |

In the course of grinding there was added 3.0% of N - n - propyl - *p* - menthane - 3-carboxamide. A talcum powder having a freshening and cooling effect was obtained.

## EXAMPLE XXX.

*Soft Drink*

A soft drink concentrate was prepared from the following recipe:

| | |
|---|---|
| Pure orange juice | 60% |
| Sucrose | 10 |
| Saccharin | 0.2 |
| Orange flavouring | 0.1 |
| Citric acid | 0.2 |
| Sulphuric dioxide | trace amount |
| Water | to 100% |

To the concentrate was added 0.02% of N-(1,1 - dimethyl - 2 - hydroxyethyl) - *p*-menthane - 3 - carboxamide.

The concentrate was diluted with water and tasted. An orange flavour having a pleasantly cool after-effect was obtained.

## EXAMPLE XXXI.

*Alcoholic Beverage*

N - (2 - hydroxy - n - propyl) - *p* - menthane - 3 - carboxamide was added to a proprietary gin in an amount of 0.8%. When tasted a very strong cooling after-effect is obtained in the mouth.

## EXAMPLE XXXII.

*Boiled Sweet*

99.5% sucrose and 0.5% citric acid were carefully fused together in the presence of a trace of water. Just before casting the melt onto a chilled plate 0.13% of N,N - dimethyl - *p* - menthane - 3 - carboxamide were rapidly stirred in. The melt was then cast. A boiled sweet resulted having a marked cooling effect on the mouth.

## EXAMPLE XXXIII.

*Mint Sweet*

Water was added to icing sugar at 40° C. to form a stiff paste. 0.05% of N - ethyl - *p*-menthane - 3 - carboxamide was then stirred into the paste and the mixture allowed to set. A soft sweet mass resulted having the characteristic cooling effect in the mouth of peppermint but without the minty flavour or odour.

## EXAMPLE XXXIV.

*Chewing Gum*

Leaves of a proprietary chewing gum were leached in running water for 168 hours to remove all water-soluble flavourants. At the end of the leaching operation the chewing gum base had no detectable minty odour or flavour. The chewing gum base was then kneaded with 5.0% of N,N - bis(2 - hydroxyethyl) - *p*-menthane - 3 - carboxamide. When compared with the water-extracted chewing gum base,

the final product showed no distinguishable change in flavour but showed a marked cooling effect in the mouth.

## EXAMPLE XXXV.

*Ice-Cream*

A proprietary ice cream mixture was mixed in accordance with the manufacturers instructions. Shortly before freezing N - *p* - menth-3 - oyl - *β* - aminopropionic acid n-propyl ester was added in an amount of 0.05%. When sampled a cooling effect is noticeable which persists after the cooling effect attributable to the temperature of the ice cream has disappeared.

## EXAMPLE XXXVI.

*Indigestion tablet*

The following ingredients were ground together:

| | |
|---|---|
| Magnesium carbonate | 49.5% |
| Sorbitol | 49.4% |
| Saccharin | 0.1% |
| Talc | 1.0% |

Added to the mixture during grinding was 0.05% of N - ethyl - *p* - menthane - 3 - carboxamide. After mixing the mixture was pressed into 0.5 g tablets.

Taken by mouth and swallowed the tablets produces after a short interval of time a noticeable cooling effect in the stomach.

## EXAMPLE XXXVII.

*Antiseptic Ointment*

An ointment was prepared according to the following formulation:

| | |
|---|---|
| Cetyltrimethyl ammonium bromide | 4.0% |
| Cetyl Alcohol | 6.0% |
| Stearyl Alcohol | 6.0% |
| White Paraffin | 14.0% |
| Mineral Oil | 21.0% |
| Water | to 100% |

The ingredients were mixed, warmed to 40° C. and emulsified in a high speed blender. Added to the mixture during blending was 0.5% N - (*p* - menth - 3 - oyl) glycine methyl ester.

The final ointment when applied to the skin gave rise to a marked cooling effect.

## EXAMPLE XXXVIII.

*Antipruritic Ointment*

The following ingredients were warmed together to form a homogenous melt:

| | |
|---|---|
| Methyl salicylate | 50.0% |
| White Beeswax | 25.0% |
| Anhydrous lanolin | 25.0% |

To the melt was added 0.1% of N - (*p*-menth - 3 - oyl)glycine n-propyl ester and the mixture then allowed to solidify. A soft ointment resulted having a soothing effect on the skin accompanied by a noticeable cooling effect.

## EXAMPLE XXXIX.

*Analgesic tablet*

Soluble aspirin (calcium acetylsalicylate) tablets were impregnated with 0.05% of N-ethyl - *p* - menthane - 3 - carboxamide by absorption in the tablet of a metered drop of an ethanolic solution of the carboxamide. When a tablet was swallowed a quite noticeable cooling effect developed in the stomach after a short interval.

## EXAMPLE XL.

*Cleansing Tissue*

A cleansing liquid was prepared having the formulation:

| | |
|---|---|
| Triethanolamine Lauryl sulphate | 1.0% |
| Glycerol | 2.0% |
| Perfume | .95% |
| Water | to 100% |

To this liquid was added 1.0% of N - ethyl-*p* - menthane - 3 - carboxamide. A paper tissue was then soaked in the liquid.

When the impregnated tissue was used to wipe the skin a fresh cool sensation developed on the skin after a short interval.

The experiment was repeated using 2.0% of N - 3 - hydroxypropyl - *p* - menthane carboxamide in place of the N-ethyl compound with equally effective results.

## EXAMPLE XLI.

*Water-soluble Adhesive*

A solution was made up containing 5% gum acacia in water. To this solution was added 0.025% of N - ethyl - *p* - menthane - 3-carboxamide. The solution was then coated on a label and allowed to dry. Licking the label to regain the tack prior to affixing the label to a substrate gave a pleasant cooling sensation on the tongue.

The above Examples illustrate the range of compounds and the range of compositions included within the present invention. However, they are not to be taken as limiting the scope of the invention in any way. Numerous other compounds within the general formula will be equally suitable for use in the compositions of Examples XVII—XLI and the physiological cooling effect obtained with the compounds of the invention will recommend their use in a wide variety of other compositions where the cooling effect will be of value.

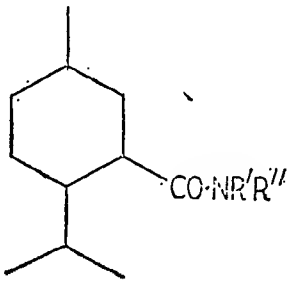
*Toxicology and Dermatology*

Toxicological studies on the compounds of

this invention have shown that the compounds are substantially non toxic, $LD_{50}$ levels in mice being higher than 2g/kg. Enclosed patch tests on the skin, on both rabbits and humans, have shown an extremely low level of allergic response even in persons known to be extremely susceptible to skin allergies. Eye tests on rabbits have also shown that the compounds of the invention are substantially free of ocular irritancy.

WHAT WE CLAIM IS:—

1. N - substituted - *p* - menthane - 3-carboxamides of the formula




where

R', when taken separately, is hydrogen or an aliphatic radical containing up to 25 carbon atoms;

R'', when taken separately is hydroxy, or an aliphatic radical containing up to 25 carbon atoms, with the proviso that when R is hydrogen R'' may also be an aryl radical of up to 10 carbon atoms and selected from substituted phenyl, phenalkyl or substituted phenylalkyl, naphthyl and substituted naphthyl, and pyridyl; and

R' and R'' when taken together, represent a cyclic or heterocyclic group of up to 25 carbon atoms.

2. Compounds according to claim 1, where R', when taken separately, is hydrogen, $C_1$—$C_9$ straight or branched chain alkyl, $C_1$—$C_4$ straight or branched chain hydroxyalkyl or aminoalkyl or a $C_1$—$C_4$ acylated derivative thereof, or $—C_nH_{2n}COR'''$ or $—C_nH_{2n}COOR'''$ where $—C_nH_{2n}$ is a straight or branched chain alkylene group in which n is an integer of from 1—6 and R''' is hydrogen or $C_1$—$C_8$ alkyl or $C_1$—$C_8$ hydroxyalkyl; R'', when taken separately, is an organic group as defined above for R', R' and R'' being the same or different; and R' and R'', when taken together, represent an alkylene chain optionally interrupted by oxygen and forming, together with the nitrogen atom to which R' and R'' are attached, a 5- or 6-membered ring.

3. Compounds according to claim 1, where R' and R'' are both alkyl of 1—3 carbon atoms.

4. N,N - dimethyl - *p* - menthane - 3-carboxamide.

5. N,N - diethyl - *p* - menthane - 3-carboxamide.

6. Compounds according to claim 1, where R' is hydrogen and R'' is alkyl of 1—3 carbon atoms, hydroxyalkyl of 1—4 carbon atoms or $—CH_2COOR'''$, where R''' is alkyl of 1—4 carbon atoms.

7. N - *p* - menth - 3 -oylglycine n-propyl ester.

8. N - ethyl - *p* - menthane - 3 - carboxamide.

9. N - (1,1 - dimethyl - 2 - hydroxyethyl) - *p* - menthane - 3 - carboxamide.

10. N - (3 - hydroxypropyl) - *p* - menthane - 3 - carboxamide.

11. N - *p* - menth - 3 - oylglycine ethyl ester.

12. A composition capable of stimulating the cold receptors of the human body, comprising an effective amount of a cold receptor stimulant and a carrier therefor, said stimulant comprising one or more N - substituted - *p*-menthane - 3 - carboxamides of the formula defined in claim 1.

13. An ingestible composition capable of stimulating the cold receptors of the nerve endings of the mucous membranes of the mouth and gastrointestinal tract comprising an edible carrier and an effective amount of an N - substituted - *p* - menthane - 3-carboxamide of the formula defined in claim 1.

14. A composition for topical application to the human body and capable of stimulating the cold receptors of the nerve endings in the skin comprising a pharmaceutically acceptable carrier and an effective amount of an N - substituted - *p* - menthane - 3 - carboxamide as claimed in claim 1.

15. A cleansing tissue comprising a fibrous carrier impregnated with a liquid containing an effective amount of a cold receptor stimulant, said stimulant comprising one or more N - substituted - *p* - menthane - 3-carboxamides of the formula defined in claim 1.

16. A chewing gum composition capable of stimulating the cold receptors of the nerve endings of the oral mucous membranes and comprising a compound according to any one of claims 1—11.

17. A toothpick impregnated or coated with an effective amount of a cold receptor stimulant, said stimulant comprising one or more of N - substituted - *p* - menthane - 3 - carboxamides of the formula defined in claim 1.

18. A comestible composition comprising an edible base, a flavourant or colourant, and at least one of the following:

N - methyhl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (2 - hydroxypropyl) - *p* - methane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

19. A beverage comprising a potable base, a flavourant or colourant, and at least one of the following:

N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

20. A lotion comprising an aqueous, alcoholic or aqueous-alcoholic carrier, an adjuvant selected from the following: a colourant, an antiseptic or an odourant, and a cold receptor stimulant selected from the following:

N,N - dimethyl - *p* - menthane - 3-carboxamide;
N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

21. A dentifrice comprising an abrasive, a deteragent or foaming agent and at least one of the following:

N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

22. A toilet preparation comprising an oleaginous base and at least one of the following:

N,N - dimethyl - *p* - menthane - 3 - carboxamide;
N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

23. A pharmaceutical preparation comprising an antacid and at least one of the following:

N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

24. A toilet preparation containing a soap or synthetic surfactant and at least one of the following:

N,N - dimethyl - *p* - menthane - 3 - carboxamide;
N - methyl - *p* - menthane - 3 - carboxamide;
N - ethyl - *p* - menthane - 3 - carboxamide;
N - (2 - hydroxyethyl) - *p* - menthane - 3-carboxamide;
N - (3 - hydroxypropyl) - *p* - menthane - 3-carboxamide;
N - *p* - menth - 3 - oylglycine ethyl ester;
N - (1,1 - dimethyl - 2 - hydroxy ethyl)-*p* - menthane - 3 - carboxamide;
N - *p* - menth - 3 - oylglycine *n*-propyl ester.

25. A composition according to claim 12, substantially as hereinbefore described in any one of Examples XVII—XLI.

26. A method of stimulating the cold receptors of the nervous system of the skin and mucous membranes of the human body, other-

wise then for medical purposes, which comprises applying to the skin or mucous membranes a compound as claimed in claim 1.

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